REMARKS

1. The antecedent basis problems of claims 13 (SID 5), 14 (SID 6), 16 (SID 8) and 17 (SID 9) have been cured by amending claim 8 to recite those sequences. SID 6, 8 and 9 have been added to clause (a), and SID 5 to new clause (e).

2. Improper multiply dependent claim 44 (dependent conjunctively on claims 1 and 8, hence improper even if claim 1 hadn't been withdrawn) has been corrected by striking the reference to claim 1 and instead reciting claim 1's limitations directly within 44.

3. The written description rejection based on the recitation in claim 8 (I)(d) of "or comprises a sequence at least 50% identical to a peptide of (a)" is addressed by replacing 50% with 90%, with basis at P20, L31.

The reference sequences recited by claim 8 are as follows:

SID	Length
*1	13
2	14
4	9
7	10
10	14
11	5
12	12
13	9
14	9
16	16
17	12
18	11
40	13
*41	14
5	3
6	7
8	10
9	5

With only 10% divergence allowed, the smallest reference sequence into which even a single amino acid can be introduced per amended (d) is 10 aa, and even then only a single

substitution mutant could satisfy "at least 90%".

4. Claim 8 is rejected as anticipated by Small et al. (1987)'s NCAM, an 856 aa polypeptide which is said to comprise (and therefore allegedly qualify as "100% identical to") instant SEQ ID NOs:1, 2, 4-6, 8, 9 and 11-26.

The examiner says that the rejected claim recites "having", which the examiner interprets as "comprising". However, we are unable to find any occurrence of this word in claim 8.

We now compare the compounds of claim 8 with NCAM in more detail.

I(a): these peptides are the recited peptides, with lengths not exceeding 14 aa, and plainly not anticipated by NCAM.

I(b): these are fragments of (a), hence smaller, likewise not anticipated.

I(c): these consist of the peptides of (a) and up to 10 additional amino acids, thus up to 24 aa in length. This is still well short of NCAM.

(I(d): these are peptides which differ from (a), (b) or (c) "solely by one or more amino acid substitutions". Substitutions do not lengthen the peptide and hence the maximum length is 24 aa.

These peptides of (d) are subject to a further constraint as to the nature of the substitutions. Either they must leave a five amino acid fragment of (a) intact, or comprise a sequence at least 90% (formerly 50%) identical to a peptide of (a).

It has occurred to us that the examiner may have interpreted (d) incorrectly, so the "comprises a sequence at least 50% identical" was deemed an alternative to the rest of (d) and not merely to "at least a five amino acid fragment of a peptide of (a)". We had thought the subsidiary nature of these constraints was clear from the "but", but for the sake

of clarity we label the secondary constraints as "(d1)" and "(d2)".

Clause (II) covers polymers comprising a plurality of peptides according to clause (I). While this condition might be met by NCAM, it further provides that it "either consists of a plurality of peptides according to (I) above, or comprises a non-NCAM carrier moiety to which said peptides are attached. NCAM cannot satisfy either limitation.

5. We have cancelled group I (1-7) and IV (43). We respectfully submit that group III claims (30-39 and 42) may now be rejoined.

6. Claim 8 has been amended to require that the compound be purified with basis at P60, L26; P61, L7; P77, L26; note that in the preferred embodiment they were sufficiently pure for their N-termini to be sequenceable (P77, L32).

New claim 69 requires that the compound be in soluble form, with basis at P28, L3-5 and 26-31 (the reference to the Ig1-2-3 module being in solution is believed to also apply to the fragment); P45, L9, 16-17, 32-33; P60, L22-25 (if the "proteinaceous components" are precipitated from the culture medium, it implies they were dissolved therein); P62, L25.

The purpose of these limitations is to avoid any possibility of inherent anticipation by an unselected peptide in a prior art peptide library. Combinatorial libraries are alluded to at P43, L29 (basis for new claim 70).

The general rule concerning inherent anticipation is that the allegedly inherent feature must be certain to be present in view of the explicit features. See Ex parte Levy, 17 USPQ2d 1461, 1464 (BPAI 1990) ("inherent characteristic necessarily flows" from prior art teachings); Glaxo Inc. v. Novopharm Ltd., 29 USPQ2d 1126 (EDNC 1993), aff'd 34 USPQ2d 1565 (Fed. Cir. 1995) (allegedly inherent result must "invariably" happen); Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc., 32 USPQ2d 1017, 1020 (Fed. Cir. 1994)

(that a thing "may result" is insufficient); Motorola, Inc. v. Interdigital Technology Corp., 930 F. Supp. 952, 970 (D. Del. 1996); Marion Merrell Dow Inc. v. Geneva Pharmaceuticals, 33 USPQ2d 1673, 1677 (D. Col. 1994); Hughes Aircraft Co. v. United States, 8 USPQ2d 1580, 1583 (Claims Ct. 1988) (in anticipation-by-inherency cases, the element must "flow undeniably and irrefutably from the express disclosures"); Ethyl Molded Products Co. v. Betts Package, Inc., 9 USPQ2d 1001, 1032-3 (E.D. Ky. 1988) (doctrine requires "certainty"; "probabilities are not sufficient"); Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ2d 1065, 1076-77 n. 12 (D. Del. 1987), aff'd 9 USPQ2d 1461 (Fed. Cir. 1989) ("anticipation...cannot be predicated on mere conjecture").

Peptide libraries usually do not much exceed 10^8 different sequences. To inherently anticipate a hexapeptide, a hexapeptide library would have to have a size of $20^6 = 3.2 \times 10^8$ members, so that it at least theoretically includes all possible hexapeptides. As the potential diversity of a library increases beyond 10^8 and even more so beyond 10^9 or 10^{10}, it may outstrip the size of the library, i.e., the ability of the library to represent the entire sequence space. We do not think it possible for a peptide library of the prior art to have inherently anticipated peptides of 10+ aa (such as SEQ ID NOs:1, 7 and 40) as that would require that it include all 20^{10}, i.e. about 10^{12}, different decapeptides, or even more of longer peptides.

Hence, our concerns are chiefly directed to SID 5(3 aa), SID 9 and 11(5 aa), and SID 6(7 aa), and possibly to SID 4, 13 and 14(9 aa). (This should not be construed as an admission that any prior art library of the indicated size in fact is inherently anticipatory.)

Peptide libraries may be characterized as falling into the following general categories:

Soluble (tea-bag) libraries: Houghton and Rutter created

libraries comprising, e.g., 20 "tea-bags"; all of the peptides in a given bag having the same N-terminal AA but varying otherwise, and the N-terminal AA differing from bag to bag. If a bag were found positive, 20 sublibraries (with the N-terminal AA constant for all, the 2nd AA varies from bag to bag, and the rest being random) were synthesized. By screening even more biased libraries, the active sequence could ultimately be recovered ("deconvoluted").

It should be clear that the peptides of these libraries are not purified.

Phage libraries: Random inserts are introduced into phage, so each phage particle displays a single peptide on its surface, the sequences varying from particle to particle. There is no purification until a phage particle is physically separated from the other particles on account of displaying a peptide with a screened- or selected-for binding property. Moreover, the peptide in the library is not in soluble form.

Bead libraries: In the split-and-mix method, beads are divided into 20 aliquots, each reacted with a single AA, and recombined. The process is repeated until the entire peptide is synthesized. The result is that each bead holds only peptides of a single sequence, but sequences vary from bead to bead.

In our opinion, there is no purification of a peptide until a bead bearing that peptide is physically separated from the other beads, which of course happens to only a few beads (those displaying the desired binding properties). Moreover, the peptides in the library are not in soluble form.

Finally, there is the so-called spatially addressable library of Fodor. Photochemical reactions, with masking, are used to control which sequences are synthesized depending on the peptides' "grid locations". As far as we know, this method has only been used to synthesize dipeptides. Hence, even if the physical separation between grid intersections was

deemed a "purification" (which we contest), it would not inherently anticipate. Moreover, the peptides on Fodor's support are not in soluble form.

For the sake of completeness, we also cite the work of Geysen. Geysen synthesized single substitution mutants of epitopes on pins. Absent reason to be certain that one of our peptides is identical to, or a single substitution mutant of, an epitope so studied in the prior art, there is no inherent anticipation.

New claim 71 requires that the peptide of I(a) be one of SEQ ID NOs:1, 7 or 40. Note that this does not require that the compound of claim 71 be the one of these sequences, but rather it be them or a sequence of (I)(b)-(d) or (II) having the specified relationship to SID1, 7 or 40. New claims 72-91 parallel 46-68 but are dependent on 71.

Respectfully submitted,

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